PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

**Thomas S.Y. KO et al**

Appln. No.: **Not Yet Assigned** Group Art Unit: **0000**

Filed: **January 25, 2002** Examiner: **Unknown**

For: **METHOD OF PREPARING BIOLOGICAL MATERIALS AND PREPARATIONS PRODUCED USING SAME**



## PRELIMINARY AMENDMENT

Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examining the above-identified application, please amend the application as follows.

**IN THE CLAIMS**:

Please amend the claims as follows:

Claim 1. (Amended) A method of preparing products comprising moisture-sensitive biologically active ingredients comprising at least the steps:

(i) providing a coating liquid comprising at least one moisture-sensitive biologically active ingredient, a sugar polymer and a water soluble/miscible solvent;

(ii) providing microparticles comprising at least water soluble gel forming solid particles;

(iii) fluidizing said microparticles within a processing chamber of a suitable apparatus to form a fluidized bed of said microparticles;

(iv) spraying said coating liquid onto said fluidized bed from beneath the fluidized bed to coat said microparticles with said coating liquid under saturated moisture conditions; and

(v) allowing the resulting coated microparticles to dry.

Claim 2. (Amended) The method according to claim 1, additionally comprising one or more additional coating steps to further coat the microparticles with at least one of an enteric coating, a film coating, a moisture repellant coating, and a taste-masking coating.

Claim 3. (Amended) The method according to claim 1, wherein in step (v) the resulting microparticles are heat dried.

Claim 4. (Amended) The method according to claim 1, wherein the active ingredient comprises one or more proteins, peptides or cells.

Claim 5. (Amended) The method according to claim 1, wherein the water soluble/miscible solvent is glycerol, propylene glycol, or a combination of glycerol and propylene.

Claim 6. (Amended) The method according to claim 1, wherein the sugar polymer is selected from the group consisting of dextran, fructose, fruitose, glucose, invert sugar, lactitol, lactose, maltitol, maltodextrin, maltose, mannitol, sorbitol, sucrose, trehalose, isomalt, xylitol and polydextrose, or a combination thereof.

Claim 7. (Amended) The method according to claim 1, wherein the water soluble gel forming solid particles comprise a member selected from the group consisting of acrylate or

derivatives thereof, albumin, alginates, carbomers, carrageenan, cellulose or derivatives thereof, dextran, dextrin, gelatine, polyvinylpyrrolidone and starch.

Claim 8. (Amended) The method according to claim 1, wherein the method is conducted in a moisture saturated environment.

Claim 9. (Amended) The method according to claim 1, wherein the method is conducted in an oxygen free environment.

Claim 10. (Amended) The method according to claim 1, wherein the resulting coated microparticles are formed into a composition for injection, as a sublingual tablet, as an oral tablet, as a sustained release sublingual tablet, into microcapsules, pessaries, preconstituted solid dose for nasal spray, nasal drops, aqueous drops, eye wash, eye drops, skin washing solutions or as a feed premix.

Claim 11. (Amended) The method according to claim 1, wherein said method is useful for stabilizing biologically active ingredients.

Claim 12. (Amended) The method according to claim 1, wherein the microparticles have a particle size of 50 microns to one millimeter.

Claim 13. (Amended) The method according to claim 1, wherein the active ingredient is a hormone, cytokine or growth factor or a combination of any two or more thereof.

Claim 14. (Amended) The method according to claim 13, wherein the active ingredient is selected from the group consisting of a human growth hormone, an animal growth hormone, a human growth hormone derivative, an animal growth hormone

derivative, erythropoietin, calcitonin, interferon, interleukin, insulin and a colony stimulating factor.

Claim 15. (Amended) The method according to claim 1, wherein the active ingredient is an enzyme.

Claim 16. (Amended) The method according to claim 15, wherein the enzyme is selected from the group consisting of streptokinase, muramidase, pancrease, amylase, protease, lypase, cellulase, bromelain and papain.

Claim 17. (Amended) The method according to claim 1, wherein the active ingredient is glucan.

Claim 18. (Amended) The method according to claim 17, wherein said glucan is β-1,3-glucan.

Claim 19. (Amended) The method according to claim 1, wherein the active ingredient is a microorganism.

Claim 20. (Amended) The method according to claim 19, wherein the microorganism is one or more of *Bifidus* or *Lactobacilli*.

Claim 21. (Amended) A product produced by the method according to any one of claims 1 to 20.

Claim 22. (Amended) A composition comprising a core of microparticles coated with a moisture-sensitive biologically active ingredient and sugar polymer coating layer.

Claim 23. (Amended) The composition according to claim 22, wherein said microparticles are further coated with at least one of an enteric coating, a film coating, a moisture repellent coating and a taste-masking coating.

Claim 24. (Amended) The composition according to claim 22, wherein the active ingredient comprises one or more proteins, peptides or cells.

Claim 25. (Amended) The composition according to claim 24, wherein the active ingredient is a hormone, cytokine, or growth hormone, or a combination of any two or more thereof.

Claim 26. (Amended) The composition according to claim 25, wherein the active ingredient is selected from the group consisting of a human growth hormone, an animal growth hormone, a human growth hormone derivative, an animal growth hormone derivative, erythropoietin, calcitonin, interferon, interleukin, insulin and a colony stimulating factor.

Claim 27. (Amended) The composition as claimed in claim 24, wherein the active ingredient is a microorganism.

Claim 28. The composition as claimed in claim 27, wherein the microorganism is one or more of *Bifidus* or *Lactobacilli*.

Claim 29. (Amended) The composition as claimed in claim 22, wherein the active ingredient is an antidiarrhea agent.

Claim 30. (Amended) The composition as claimed in claim 22, wherein the active ingredient is a growth promotant.

Claim 31. (Amended) The composition as claimed in claim 22, wherein said composition comprises microparticles comprising a member selected from the group consisting of acrylate or derivatives thereof, albumin, alginates, carbomers, carrageenan, cellulose or derivatives thereof, dextran, dextrin, gelatin, polyvinylpyrrolidone and starch.

Claim 32. (Amended) The composition as claimed in claim 22, wherein said composition is in the form of an injection, as a

sublingual tablet, as an oral tablet, as a sustained release sublingual tablet, microcapsules, pessaries, preconstituted solid dose for nasal spray, nasal drops, aqueous drops, eye wash, eye drops, skin washing solutions, or as a feed premix.

## REMARKS

Claims 1-32 have been amended in order to remove improper multiple dependency and make the claims consistent with U.S. patent practice. Hence, the amendments to the claims do not constitute new matter, and entry is respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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**A P P E N D I X**

Marked-Up Version of Changes

**IN THE CLAIMS**:

The claims are being amended as follows:

Claim 1. (Amended) A method of preparing products [containing] comprising moisture-sensitive biologically active ingredients [materials, including biological materials such as proteins, peptides or live cells,] comprising at least the steps:

(i) providing a coating liquid comprising at least one moisture-sensitive biologically active ingredient [active], a sugar polymer and a water soluble/miscible solvent;

(ii) providing [a quantity of] microparticles comprising at least water soluble gel forming solid particles;

(iii) fluidizing said [quantity of] microparticles within a processing chamber of a suitable apparatus to form a fluidized bed of said microparticles;

(iv) spraying said coating liquid onto said fluidized bed from beneath the fluidized bed to coat said microparticles [therewith] with said coating liquid under saturated moisture conditions; and

(v) allowing the resulting coated microparticles to dry.

Claim 2. (Amended) [A] The method according to claim 1, [wherein] additionally comprising one or more additional coating steps to further coat the microparticles with at least one of an

enteric coating, a film coating, a moisture repellant coating, [and/or] and a taste-masking coating.

Claim 3. (Amended) [A] The method according to claim 1, [or 2] wherein in step (v) the resulting microparticles are heat dried.

Claim 4. (Amended) [A] The method according to [any one of claims] claim 1, [to 3] wherein the active ingredient comprises one or more proteins, peptides[,] or cells.

Claim 5. (Amended) [A] The method according to [any one of claims] claim 1, [to 4] wherein the water soluble/miscible solvent is glycerol, propylene glycol, or a combination of glycerol and propylene.

Claim 6. (Amended) [A] The method according to [any one of claims] claim 1, [to 5] wherein the sugar polymer is selected from [a] the group [comprising] consisting of dextran, fructose, fruitose, glucose, invert sugar, lactitol, lactose, maltitol, maltodextrin, maltose, mannitol, sorbitol, sucrose, trehalose, isomalt, xylitol[,] and polydextrose, or a combination thereof.

Claim 7. (Amended) [A] The method according to [any one of claims] claim 1, [to 6] wherein the water soluble gel forming solid particles [comprising one or more water soluble gel forming solid particles] comprise a member selected from [a] the group [comprising] consisting of acrylate [and] or derivatives thereof, albumin, alginates, carbomers, carrageenan, cellulose [and] or derivatives thereof, dextran, dextrin, gelatine, polyvinylpyrrolidone[,] and starch.

Claim 8. (Amended) [A] The method according to [any one of claims] claim 1, [to 7] wherein the method is conducted in a moisture saturated environment.

Claim 9. (Amended) [A] The method according to [any one of claims] claim 1, [to 8] wherein the method is conducted in an oxygen free environment.

Claim 10. (Amended) [A] The method according to [any one of claims] claim 1, [to 9] wherein the resulting coated microparticles are formed into a composition for injection, as a sublingual tablet, as an oral tablet, as a sustained release sublingual tablet, into microcapsules, pessaries, preconstituted solid dose for nasal spray, nasal [or] drops, aqueous drops, eye wash, [or] eye drops, skin washing solutions[,] or as a feed premix.

Claim 11. (Amended) [A] The method according to [any one of claims] claim 1, [to 9] wherein [the] said [is a] method is useful for stabilizing [biological materials] biologically active ingredients.

Claim 12. (Amended) [A] The method according to [any one of claims] claim 1, [to 11] wherein the microparticles [are] have a particle size of 50 microns to one millimeter [millimetre particle size].

Claim 13. (Amended) [A] The method according to [any one of claims] claim 1, [to 12] wherein the active ingredient is a hormone, cytokine or growth factor or a combination of any two or more thereof.

Claim 14. (Amended) [A] The method according to claim 13, wherein the active ingredient is selected from the group consisting of a human growth hormone, [or] an animal growth [hormones] hormone, a human growth hormone derivative, an animal growth hormone derivative [or derivatives thereof], erythropoietin, calcitonin, interferon, interleukin, insulin[, or] and a colony stimulating factor.

Claim 15. (Amended) [A] The method according to [any one of claims] claim 1, [to 12] wherein the active ingredient is an enzyme.

Claim 16. (Amended) [A] The method according to claim 15, wherein the enzyme [comprises] is selected from the group consisting of streptokinase, muramidase, [pancreas] pancrease, amylase, protease, lypase, cellulase, bromelain[, or] and papain.

Claim 17. (Amended) [A] The method according to [any one of claims] claim 1, [to 12] wherein the active ingredient is glucan.

Claim 18. (Amended) [A] The method according to claim 17, wherein said glucan is β-1,3-glucan.

Claim 19. (Amended) [A] The method according to [any one of claims] claim 1, [to 12] wherein the active ingredient is a microorganism.

Claim 20. (Amended) [A] The method according to claim 19, wherein the microorganism is one or more of *Bifidus*[,] or *Lactobacilli*.

Claim 21. (Amended) A product [when] produced by [a] the method according to any one of claims 1 to 20.

Claim 22. (Amended) A composition comprising a core of microparticles coated with [an] a moisture-sensitive biologically active ingredient and sugar polymer coating layer.

Claim 23. (Amended) [A] The composition according to claim 22, [which is] wherein said microparticles are further coated with at least one of an enteric coating, a film coating, a moisture repellent coating[,] and a taste-masking coating[, or one or more such coatings].

Claim 24. (Amended) [A] The composition according to claim 22, [or 23] wherein the active ingredient comprises [a protein, peptide, or cell] one or more proteins, peptides or cells.

Claim 25. (Amended) [A] The composition according to claim 24, wherein the active ingredient is a hormone, cytokine, or growth hormone, or a combination of any two or more thereof.

Claim 26. (Amended) [A] The composition according to claim 25, wherein the active ingredient is selected from [a] the group [comprising] consisting of a human growth hormone, [or] an animal growth [hormones] hormone, a human growth hormone derivative, an animal growth hormone derivative [or derivatives thereof], erythropoietin, calcitonin, [and] interferon, [and] interleukin, insulin[,] and a colony stimulating factor.

Claim 27. (Amended) [A] The composition as claimed in claim 24, wherein the active ingredient is a microorganism.

Claim 28. [A] The composition as claimed in claim 27, wherein the microorganism is one or more of *Bifidus*[,] or *Lactobacilli*.

Claim 29. (Amended) [A] The composition as claimed in [any one of claims] claim 22, [to 24] wherein the active ingredient is an [antidiarrhoea] antidiarrhea agent.

Claim 30. (Amended) [A] The composition as claimed in [any one of claims] claim 22, [to 24] wherein the active ingredient is a growth promotant.

Claim 31. (Amended) [A] The composition as claimed in [any one of claims] claim 22, [to 30 which] wherein said composition comprises microparticles comprising a member selected from the group consisting of acrylate[,] or derivatives thereof, albumin, alginates, carbomers, carrageenan, cellulose[,] or derivatives

thereof, dextran, dextrin, gelatin, polyvinylpyrrolidone[, or] and starch.

Claim 32. (Amended) [A] The composition as claimed in [any one of claims] claim 22, [to 31] wherein said composition is in the form of an injection, as a sublingual tablet, as an oral tablet, as a sustained release sublingual tablet, microcapsules, pessaries, preconstituted solid dose for nasal spray, nasal [or] drops, aqueous drops, eye wash, [or] eye drops, skin washing solutions, or as a feed premix.